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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/393,590	09/09/1999	ELIZABETH MOYER	00211-US-NEW	2967

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EXAMINER	
HURT, SHARON L	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,590	MOYER ET AL.	
	Examiner	Art Unit	
	Sharon Hurt	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,7-14,16,29-39,41-47 and 49-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7-14,16,29-39,41-47 and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Nov 30, 2005*, 4/25/2006
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendments to the claims filed on 10, 2006 are acknowledged.

Status of Claims

Claims 1, 4, 7-14 and 16 are currently amended. Claims 2-3, 6, 15, 17-28, 40 and 48 are cancelled. Claims 1, 4-5, 7-14, 16, 29-39, 41-47 and 49-53 are pending and under examination.

Claim Rejections

All previous grounds of rejections are hereby withdrawn. New grounds of rejection are as follows.

Claim Objections

Claims 1 and 7 are objected to because of the following informalities: Claim 1 has a grammatical error in the 6th line of the claim. The word "and" should be inserted in the phrase "botulinum toxin suitable for use in humans an excipient protein". Claim 7 depends from a claim cancelled by applicant. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5, 7-14,16, 29-39, 41-47, and 49-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendment of the claims to recite "ready-to-use" introduces new matter as there is no support in the specification as originally filed for the phrase "ready-to-use"; There is no guidance in the specification as to the meaning of "ready-to-use". While the specification discloses that the claimed compositions are in liquid form (see page 3, lines 13-14, for example) it discloses that the liquid form may be either in diluted or in concentrated form (see page 7, lines 21-22, for example). It is not clear if "ready-to-use" is meant to encompass both the concentrated form and the diluted "working" preparation or whether it is only meant to encompass the diluted preparation. Therefore, the phrase "ready-to-use" is not either explicitly or implicitly taught in the specification. It is thus the Examiners position that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the instant application.

Claim 4 recites the buffer pH as "5.6 ±0.2", which range is not described in the specification. The term "buffer" is described in the specification as well as the buffering

capacity over a range that is within ± 1 pH on page 7 of the specification. The stable botulinum toxin formulation is characterized by a pH between about pH 5 to 6, preferably about pH 5.5-5.6 on page 13 of the specification. There is no support in the specification for the specific pH range of 5.6±0.2 for the buffered formulation. Therefore, a person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed.

Therefore, the new limitations in the claims listed above are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c). Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the new limitations, or to remove the new matter from the claims(s).

Claims 1, 4-5, 7-13, 29-39, 41-47 and 49-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a botulinum toxin formulation that is stable in liquid form for at least two years at a temperature of about 5°C (or for at least 6 months at 10-30°C) in succinate buffer at a pH of about 5.6 with recombinant human serum albumin as an excipient, does not reasonably provide enablement for a botulinum toxin formulation in buffers other than succinate buffer, at pH levels above or below about 5.6, or with excipients other than recombinant human serum albumin that is stable in liquid form for at least two years at "about 0 and 20

degrees centigrade". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those In the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The instant invention is drawn to a stabilized liquid pharmaceutical botulinum formulation for therapeutic use in humans comprising a therapeutic concentration of a purified botulinum toxin; an excipient protein selected from serum albumin, recombinant human serum albumin, and gelatin; and a pharmaceutically acceptable buffered saline that is capable of providing a buffered pH range between pH 5 and 6; wherein the buffer is selected from phosphate buffer,

phosphate-citrate buffer, and succinate buffer and wherein the formulation is stable up to two years .

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the stability of botulinum toxins in liquid form is unpredictable and varies based on the type of buffer used, the pH, the temperature used for storage, and excipient protein. Goodnough et al. (Applied and Environmental Microbiology, Oct. 1992, 3426-3428) teach that a commercially available lyophilized product, diluted and lyophilized at pH 7.3 in a diluent containing sodium chloride and human serum albumin, is unpredictable in its stability depending on the buffer used to reconstitute the preparation (see page 3426, second paragraph, and page 3427, last sentence of the second paragraph). Goodnough et al. further teach that excipient proteins vary in stabilizing effect and that some stabilizing excipients, such as human serum albumin derived from blood and gelatin, are contraindicated due to the possibility of blood contaminants or pyrogens (see page 3427, last paragraph). Gartlan et al. (Otolaryngol Head Neck Surg. Nov. 1993, Vol. 108, No. 2, pages 135-140) teach that the choice of diluent, buffer, pH and storage temperature all have profound effects on the stability of liquid preparations (see page 139, second paragraph though seventh paragraph). Finally, Gartlan et al. teach that since therapeutic concentrations of a botulinum toxin are very unstable in liquid form, the FDA recommends that liquid preparations of the commercially available lyophilized toxin be discarded after just 4 hours (see the abstract). McLellan et al. (Toxicon, 1996, Vol. 34, No. 9, pages 975-985) teach that different formulations of toxin differ in potency as a result of the choice of the diluent

used to prepare the clinical preparations and the storage temperature (see the abstract, last sentence, page 979, first paragraph, and the paragraph bridging pages 979-981).

The amount of direction or guidance present and the presence or absence of working examples important parameters in achieving successful therapy:

Given the teachings of unpredictability in the art regarding the stability of liquid formulations of botulinum toxin based on choice of buffer, pH, choice of excipient protein, and storage temperature, detailed teachings are required to be present in the disclosure in order to enable the full scope of the claims. Applicant's disclosure is limited to the formulation described in Example 1 and Table 1 on pages 20-21, which is a liquid formulation prepared in succinate buffer at pH 5.6 with recombinant human serum albumin as an excipient protein which was stable at 5°C for 30 months and was stable at about 25°C for 6 months (see pages 20-22 of the instant specification). There is no disclosure in applicant's specification of any other combination of buffer, pH, and excipient protein that stabilized a liquid preparation for at least a year at 0-10°C or for 6 months at 10-30°C. There is no disclosure of stability of the liquid formulation at temperatures other than about 5°C or about 25°C

The breadth of the claims and the quantity of experimentation needed:

Because the invention encompasses liquid pharmaceutical compositions of botulinum toxin with different buffering components, different pHs, and different excipient proteins; because the art teaches unpredictability in the stabilizing properties of different buffers, different pHs, and different excipient proteins; and because the specification fails to provide guidance as to how to make and use formulations

comprising buffers other than succinate, a pH other than about 5, and excipient proteins other than recombinant human serum albumin and because the specification fails to teach how long the liquid preparations may be stored at temperatures other than about 5°C and about 25°C, , it would require undue experimentation by one of skill in the art to be able to practice the claimed invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 contains the following language: "an excipient protein comprising serum albumin". "Comprising" is defined as "to include" which could be interpreted as including albumin in addition to other components. Therefore the phrase fails to particularly point out the composition and subject matter of the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Hurt whose telephone number is 571-272-3334. The examiner can normally be reached on M-F 8:00 - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharon Hurt

September 30, 2006

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